MICROWAVE ASSISTED SYNTHESIS OF 5-ARYL-THIOPHENE-2-CARBOXYLATES

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Abstract

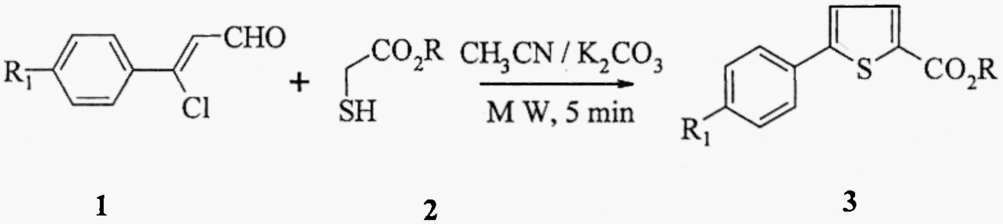
A simple and rapid method for the synthesis of 5-Aryl-thiophene-2-carboxylates **3** has been developed by the condensation of β-chlorovinyl aldehydes **1** with mercaptoacetic acid esters **2** under microwave irradiation conditions.

Introduction

Thiophenes are of considerable interest due to their application as pharmaceutical agents. A number of substituted thiophene derivatives have been reported as anti hypertensive, antiprotozoal, antibacterial,[1] antifungal, and anti-inflammatory[2] agents. 5-Arylthiophene-2-carboxylates find their application in the synthesis of immuno-suppressive,[3] antifungal[4] and flourescence[5] intermediates.

Results and Discussion

5-Arylthiophene-2-carboxylates can be synthesized by the reaction of either β-chlorovinyl aldehydes[6] or 1-chloropropen-3-ylideneimmonium salts[7] with mercapto-acetates in presence of triethylamine in pyridine and in triethylamine/pyridine in presence of potassium hydroxide[5] to effect spontaneous cyclization of the intermediate thioesters. Microwave assisted organic reactions have gained much importance during recent years, as they are completed in a short time with higher yields and purity when compared to conventional heating.[8] In continuation of our interest, in synthesizing functionally substituted heterocycles by simple methods and using commonly available reagents,[9, 10] we report here in a simple and rapid microwave assisted synthesis of 5-arylthiophene carboxylates from 3-chlorovinyl aldehydes and mercaptoacetic acid esters.



SCHEME-1

5-Arylthiophene-2-carboxylates were obtained in good yields when a mixture of β-chlorovinyl aldehydes **1** with mercaptoacetates **2** in acetonitrile in presence of potassium carbonate was subjected to microwave irradiation. All the reactions were carried out in open Erlenmeyer flask using pulse irradiation technique (one min irradiation with 2 min interval for cooling). The course of the reaction was monitored by TLC and the conversion was completed within a short period of 5 minutes when compared to conventional heating which took 2-3 hrs under reflux conditions. The structures of the compounds reported in Table –1 have been established by IR and ^1H NMR spectra and melting points were compared with authentic samples.

In conclusion, the microwave assisted synthesis of 5-arylthiophene-2-carboxylates reported herein, is a simple, clean and rapid method using inexpensive and environmentally friendly reagents with higher yields and purity.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin Elmer system 2000 FT IR spectrometer in KBr pellets. ^1H NMR spectra were recorded on a Varian 200 MHz instrument with TMS as internal standard and in $CDCl_3$. Chemical shifts were expressed in δ ppm.

General Procedure

Synthesis of 5-Aryl-thiophene-2-carboxylic acid esters:

1. **Thermal condition:** To a mixture of β-chlrovinyl aldehyde **1** (0.01 mol) ethyl or methyl mercaptoacetate (0.01 mol) in acetonitrile (10 ml) and anhydrous potassium carbonate (0.012 mol) were added. The reaction mixture was refluxed for 2-3 hrs. At the end of the reaction, as monitored by TLC, the reaction mixture was filtered, solvent removed and the residual solid was recrystallized from methanol to give pure **3**.

2. **Microwave condition:** A mixture of β-chlorovinyl aldehyde **1** (0.01 mol), ethyl or methyl mercaptoacetate (0.01 mol), anhydrous potassium carbonate (0. 012 mol), acetonitrile (10 ml) taken in a 250 ml Erlenmeyer flask was irradiated in a domestic microwave oven for 5 min (5 x 1 min with 2 min intervals). After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated in Vacuo and the residue was recrystallized from methanol to give pure **3** as crystalline solids (In case of **3a**, the residue was diluted with water and taken up in DCM as the product is oil).

The IR, ^1H NMR and spectral data of the products (**3c-l**) are given below.

Compound 3c: IR (KBr): 1675cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.29 & 7.80(m, each 2H), 7.72(d, 1H), 7.25(d, 1H), 3.95(s, 3H), MS m/z 263 (M^+).

Compound 3d: IR (KBr): 1680cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.28(m, 2H), 7.81(m, 3H), 7.41(d, 1H), 4.42(q, 2H), 1.48(t, 3H), MS m/z 277 (M^+).

Table 1. Microwave assisted Synthesis of 5-Aryl-thiophene-2-carboxylates **3**

Compd.	R	R_1	Time MW (min)	Conventional (hrs)	Yield %	M.p °C	M.p(lit) °C
3a	CH_3	H	5	4	76	96-98	
3b	C_2H_5	H	5	4	62	Oil	Oil[6]
3c	CH_3	NO_2	5	2	74	180-182	182[12]
3d	C_2H_5	NO_2	5	2	76	162-164	
3e	CH_3	OCH_3	5	4	69	127-129	
3f	C_2H_5	OCH_3	5	4	71	74-76	77[11]
3g	CH_3	SCH_3	5	3	59	136-138	
3h	C_2H_5	SCH_3	5	3	62	82-84	
3i	C_2H_5	Cl	5	2	73	81-83	83[6]
3j	C_2H_5	Br	5	2	72	79-81	79-80[6]
3k	CH_3	F	5	2	67	86-88	
3l	C_2H_5	F	5	2	65	74-76	

C, H & N Analytical data of 5-Aryl-thiophene-2-carboxylates presented in Table –1

	Mol. Formula	C Found (calc)	H Found (calc)	N Found (calc)
3a	$C_{12}H_{10}O_2S$	66.25 (66.05)	4.42 (4.58)	
3b	$C_{13}H_{12}O_2S$	67.46 (67.24)	5.43 (5.17)	
3c	$C_{12}H_9NO_4S$	53.37 (54.75)	3.66 (3.42)	5.46 (5.32)
3d	$C_{13}H_{11}NO_4S$	56.25 (56.31)	4.12 (3.97)	5.23 (5.05)
3e	$C_{13}H_{11}O_3S$	63.42 (63.15)	4.76 (4.45)	
3f	$C_{14}H_{13}O_3S$	64.62 (64.36)	5.02 (4.98)	
3g	$C_{13}H_{11}O_2S_2$	59.45 (59.31)	4.37 (4.18)	
3h	$C_{14}H_{13}O_2S_2$	60.76 (60.64)	4.76 (4.69)	
3i	$C_{13}H_{11}ClO_2S$	58.68 (58.53)	4.35 (4.12)	
3j	$C_{13}H_{11}BrO_2S$	50.46 (50.32)	3.76 (3.54)	
3k	$C_{12}H_9FO_2S$	61.37 (61.04)	4.03 (3.81)	
3l	$C_{13}H_{11}FO_2S$	62.76 (62.52)	4.67 (4.40)	

Compound 3e: IR (KBr): 1680cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.74(d, 1H), 7.56(d, 2H), 7.18(d, 1H), 6.94(d, 2H), 3.90(s, 3H), 3.84(s, 3H), MS m/z 247 (M^+).

Compound 3f: IR (KBr): 1688cm^{-1}; ^{1}H NMR ($CDCl_3$): 7.76(d, 1H), 7.57(d, 2H), 7.21(d, 1H), 6.95(d, 2H), 4.43(q, 2H), 1.49(t, 3H), MS m/z 261 (M^+).

Compound 3g: IR (KBr): 1670cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.75(d, 1H), 7.56(d, 2H), 7.27(d, 2H), 7.24(d, 1H), 3.94(s, 3H), 2.52(s, 3H), MS m/z 263 (M^+).

Compound 3h: IR (KBr): 1680cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.74(d, 1H), 7.54(d, 2H), 7.26(d, 2H), 7.23(d, 1H), 4.36(q, 2H), 2.51(8, 3H), 1.38(t, 3H), MS m/z 277 (M^+).

Compound 3i: IR (KBr): 1675cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.72(d, 1H), 7.51(d, 2H), 7.34(d, 2H), 7.18(d, 1H), 4.38(q, 2H), 1.41(t, 3H).

Compound 3j: IR (KBr): 1678cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.75(d, 1H), 7.54(d, 2H), 7.36(d, 2H), 7.21(d, 1H), 4.36(q, 2H), 1.42(t, 3H).

Compound 3k: IR (KBr): 1680cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 7.76(d, 1H), 7.63(m, 2H), 7.24(d, 1H), 7.13(m, 2H), 3.83(s, 3H), MS m/z 236 (M^+).

Compound 3l: IR (KBr): 1675cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.74(d, 1H), 7.61(m, 2H), 7.22(d, 1H), 7.12(m, 2H), 4.75(q, 2H), 1.41(t, 3H), MS m/z 250 (M^+).

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